COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2014-1)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

TITLE: **Investigating the role of the polyol pathway in the central nervous system production of fructose: an Intervention Study**

PROTOCOL NO: **2000026149**

INVESTIGATOR: **Janice Hwang, MD**
Yale University School of Medicine
300 Cedar street, TAC S-119
PO Box 208020
New Haven, CT 06520

STUDY-RELATED NO: **(203) 737-4777**

Funding Source: National Institutes of Health

Diabetic Subjects

Invitation to Participate

You are invited to take part in a research study designed to look at the effects of high blood glucose levels on the production of fructose in the brain. You have been asked to take part because you are an individual with type 1 or type 2 diabetes between the ages 18 and 65 years old.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Project

Growing evidence suggests that fructose is linked to the development of obesity and diabetes. Studies investigating the central nervous system (CNS) effects of fructose have shown that fructose and glucose, two different types of sugars, have distinct metabolic effects in the brain.

In this study, we seek to better understand a biological pathway called the polyol pathway by which fructose can be produced from glucose in the brain. We plan to use a non-invasive brain imaging technique called magnetic resonance spectroscopy (MRS). A greater understanding of the role of the polyol pathway in the brain may have important implications for understanding the effects of fructose in the human brain.

Description of Procedures

Screening visit: If you agree to participate in the study, you will have a screening visit at the YNHH Research Unit (HRU). A study doctor will take a medical history and perform a physical exam. Blood tests will be collected to ensure that you do not have any major medical problems, which would exclude you from the study. You will also undergo an oral glucose tolerance test. Female subjects will also have a urine pregnancy test prior to study participation.

Optional blood collection at the screening visit:

During the screening visit, you have the option to have an additional 50 cc of blood collected for a sub-study related to assessing the effects of diabetes and obesity on the body's immune system.

I agree to participate in the optional blood collection as described above: (initial your choice)

_____YES _____No

Intensification of Diabetes regimens: If you qualify and agree to participate in the study, you may undergo intensification of your diabetes regimen. This process will be managed by Dr. Hwang, a fully trained attending endocrinologist, and will follow the general strategies outlined in the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Additionally, you will be asked to perform self-monitoring of blood glucose (SMBG) at least 4 times a day (before breakfast, lunch, dinner, and bedtime). The daily SMBG records will be sent to Dr. Hwang weekly for review to guide adjustment of diabetes regimens. You will be in contact with Dr. Hwang via phone, email and consultation visits.

Nutrition Consultations: You will be in communication with a nutritionist regularly over the course of the 12-week study. The nutritionist will provide you with dietary counseling.

MRI/MRS (magnetic resonance imaging and spectroscopy) scanning: If you qualify medically for the study, you will return for brain MRI/MRS scanning as described below. MRI and MRS are non-invasive scans that will be used to take pictures that tell us about structures and chemicals in your brain.

MRS at week 0, and 12: At weeks 0, and 12 you will undergo a fasting MRI/MRS scanning of your brain at the Yale Magnetic Resonance Research Center (MRRC). This scan will last ~45 minutes. You will have blood work drawn at that time for glucose and hormone measurements.

Phlebotomy: The maximum amount of blood that will be drawn is approximately 549 cc or 18.5 oz over the 3 months of the study if you complete the entire study (including the optional hyperglycemic cl amp portions described below). If you agree to participate in the optional hyper glycemic portions, blood draws include: 5cc at the screening visit, 272 cc at week 0 visit, and 272cc at week 12. If you choose not to do the optional hyperglycemic clamp portion of the study, the total blood draw will be approximately 202cc or 7 oz over the course of the study. Blood draws include: 5cc at screen, 98.5cc at week 0 visit, and 98.5 cc at week 12. For reference, a typical donation at the Red Cross is 16 oz. We would advise you not to donate blood for at least 8 weeks after the completion of the study.

Optional Overnight Admissions and Hyper Glycemic Clamps at Weeks 0 and 12: You have the option to participate in an overnight stay and hyperglycemic clamp at the beginning (week 0) and end (week 12) of the study. If you choose to participate, you will arrive in the evening prior to your MRS scan day to the YNHH HRU. You will be admitted overnight. There, your diabetic medications will be held and an IV will be placed for an insulin infusion that will be adjusted to keep your blood sugar levels in the 100-110 mg/dL range, while

avoiding hypoglycemia (glucose <70 mg/dL). The insulin infusion protocol is based on the standard YNHH inpatient hospital insulin drip protocol.

The next morning, you will be taken to the MRRC for the MRS scan while your blood sugar levels are adjusted. One intravenous catheter will be placed in a vein in one arm to sample blood at different time points. A second IV will be placed in the other arm for infusion of dextrose (which is a glucose solution) at a variable rate to maintain your blood glucose levels at about 200 mg/dL for 2 hours.

A nurse experienced with working in a MRS environment will be with you at all times. A study physician will be outside the scanner during the entire study.

I agree to participate in the overnight stay and hyperglycemic clamp at weeks 0 and 12 of the study: (initial your choice)

_____YES _____No

Continuous Glucose Monitoring System (CGMS): You will wear a continuous glucose monitor for two 14-day intervals. These 14day blocks correspond to the weeks before the week 0 and week 12 MRS scans. After first placing the CGM prior to the week 0 scan, the system is removed after 14 days and then reinserted for 14 days before the week 12 MRS scan. We will monitor your interstitial (under the skin) glucose levels throughout the day with the use of a CGMS. The CGMS consists of two parts: monitor and sensor/transmitter. The small glucose sensor/transmitter, size of quarter coin, is discreet and easy to use. It connects wirelessly to the monitor (size of a mobile phone), that you should carry with you in your pocket, belt or handbag. One of the study physicians will insert the CGMS wire-like tip under your skin and attaches it to the skin with an adhesive patch. You will need to do at least two finger-stick measurements during the day as well with a glucose meter. You will need to wear the glucose sensor for 5 days while completing the food diary. The CGMS and glucose meter will be provided to you while you are participating in the study.

Questionnaires and Surveys

Throughout the study (before each MRS scan), you will be asked to fill out some questionnaires with questions about your feelings of hunger, satiety and fullness as well as some cognitive testing.

Optional Specimens for Future Storage

You are invited to allow some of your samples (called specimens) and related information to be stored (banked) for future research related to hormones involved in obesity and diabetes, and the study of other chemical pathways and metabolic diseases. This may help researchers in the future learn more about how to prevent, find and treat obesity and diabetes.

When your specimens and information are stored, we are careful to try to protect your identity from discovery by others. Your samples and information will receive a unique code. Other researchers will only receive coded samples and information and will not be able to link the code to you. Some of the researchers who will be provided the de-identified samples may not be on the current research protocol and may be at other research centers. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Your samples and related information may be stored indefinitely for future research.

Using your specimens for research will probably not help you. We do hope the research results will help people in the future.

There is a risk that your information could be misused. The chance of this happening is very small. We have protections in place to lower this risk by de-identifying the samples with your name and personal identifiers. Your specimens and information will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

The choice to take part is up to you. You may choose not to let us store and use your samples, and your care will not be affected by this decision. If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at 203-785-6222 to let them know you do not want your samples used any longer. You may choose to have your samples either destroyed or made anonymous (the code linking them to you will be destroyed). You must follow up this request with a written request, mailed to 300 Cedar Street, TAC 147S, New Haven CT 06519.

I agree to allow my samples and information to be stored and used for future research as described above: (initial your choice)

_____YES _____No

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

Hyperglycemia clamp:

The infusion of glucose to achieve hyperglycemia (~200 mg/dl) for 2 hours is not associated with any specific symptoms or significant adverse effects. This modestly high glucose level can be seen in poorly controlled diabetic patients following a meal.

The overnight infusion of insulin to normalize plasma glucose levels is normally not associated with any specific symptoms. There is a small risk that plasma glucose may fall to lower levels resulting in symptoms of hypoglycemia.

MRI/MRS:

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you has any of these symptoms.

There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information about you that you think might be important.

This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities.

The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on your scan, a radiologist will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact you, inform you of the finding regarding you, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

CGMS:
The CGMS poses no major risks to the subjects. Some individuals may experience black and blueness of the skin at the insertion site of the CGMS sensor, which resolves by itself in a few days.

Phlebotomy:
Phlebotomy can result in anemia, although the amount of blood taken for these studies should not result in clinically-significant anemia. We will check your hemoglobin level to make sure that you are not anemic before participating in this study. The total amount of blood taken for participation in this study will be approximately 18.5 ounces over a 12 week period.

Breach of Confidentiality: It is possible that an unauthorized individual may gain access to your private information. We will make every effort to keep your data safe and private. For more information about how your data is protected, please review the "Confidentiality and Privacy" paragraph on the next page.

Benefits: You may not directly benefit from your participation in this study. Subjects will be provided with FreeStyle Libre sensors throughout the study (9 sensors are provided during the 12 weeks that the study last), and FreeStyle Libre continuous glucose monitor reader. All participants will receive exercise and dietary counseling in accordance with ADA guidelines and increased frequency of medical attention to lower their blood glucose to target ranges. However, the results of this study may lead to better understanding of the pathways in the brain that are involved in obesity and diabetes.

Economic Considerations: You will be compensated up to $600 for participation in the study. The breakdown is as follows:

$ 25 for the screening visit

$50 for wearing the CGMS at week -1
$150 for overnight admission/Hyperglycemic clamp/MRS scans at week 0
$50 for wearing the CGMS at week 11
$ 325 for overnight admission/Hyperglycemic clamp/MRS scans at week 12

You will receive payments via a Bank of America pre-paid debit card. **Please note that your name, address, and telephone number will be shared with Bank of America for ePayments.** After your first payment milestone (your first study visit) you will receive a card in the mail which you will need to activate over the phone, any subsequent milestones payments will automatically add additional funds to your card.
You may also be reimbursed for incidental expenses for parking.

- 'According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.'

***Treatment Alternatives/Alternatives*:** The alternative is to decline participation in this study.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. As a participant in a clinical research study involving an outpatient visit to the Yale-New Haven Hospital (YNHH) Research Unit (HRU). It is important for you to know that if you do not already have a medical record at YNHH; one will be made for your visit. Some information related to the care given to you during this visit will become part of your YNHH medical record. For example, any laboratory test results that are sent to the YNHH lab for testing will appear in your medical record and any printed copies of your record. In addition, you need to know that when any person is admitted to the YNHH, the individual's previous medical records of other visits or admissions to YNHH become available to physicians and hospital staff in order to ensure that the best possible care can be provided to the individual during the hospital stay. Similarly, the researchers and staff of the HRU will have access to whatever information is already in your YNHH medical records such as past surgeries or medical conditions, emergency room visits, or possibly clinic visits when you are admitted to the HRU. If such access to your past medical history by researchers and staff responsible for the study is unacceptable to you, then you should not participate in the research study.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and your personal health information. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential.

All identifiable information that is obtained in connection with this study is stored in password protected secure computer data files, and will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. All of the information obtained in this study is kept in locked files and will be kept confidential. When the study is completed subject information is stored at least for 7 years in locked cabinets

within a locked storage unit that only the investigators of the study have access to. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 7 years, after which time the link will be destroyed and the data will become anonymous.

The information about your health that will be collected in this study includes:

- *Medical history*
- *Physical exams*
- *Laboratory results*
- *Imaging results*
- *Research study records and questionnaires*

Information about you and your health which might identify you may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about drugs involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, Dr. Janice Hwang
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Bank of America

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

If you decide to take part in this research study, you will be required to give us information about your **substance use/ /HIV status**. We have obtained a Certificate of Confidentiality (CoC) issued by the NIH. Once granted, the researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a participant's threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities. When the CoC is obtained, we will inform all active study participants.

Because this research is sponsored by the Department of Health and Human Services through **NIH**, staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects.

Even when a CoC is in place, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation in the research, then we may not use the CoC to withhold this information."

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments. The researchers may withdraw you from participating in the research if any of the study physicians think that it is not safe for you to participate in the study. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Janice Hwang at Yale University, 300 Cedar Street, TAC 147S, New Haven, CT 06519. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Contact for future studies

We ask for your permission to contact you for participation in future studies that our group may conduct. We may use your telephone number, your email address or your physical address to contact you.

I agree to be contacted regarding future studies I may qualify for: (Initial for choice)

_____ YES _____NO

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator*, Dr. Janice Hwang, 203-785-6222.* If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.